

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Bentwich et al.

App. No.: 10/536,560

Filing Date: November 26, 2003

§371(c) Filing Date: December 20, 2005

Art Unit: 1635

Examiner: Dana Shin

Title: Bioinformatically Detectable Group of
Novel Viral Regulatory Genes and Uses
Thereof

DECLARATION OF PROF. Alik Honigman UNDER 37 C.F.R. § 1.132

I, Alik Honigman (Ph.D.), hereby declare as follows:

1. I am currently employed as a faculty member at the virology department of the Hebrew University-Hadassah Medical School, Jerusalem, Israel. A true and correct copy of my *Curriculum Vitae* is attached to this declaration as Exhibit A. I am an author of 64 peer-reviewed scientific publications, of which about 33 are related to viral biology. I am familiar with the subject matter disclosed and claimed in U.S. Patent Application No. 10/536,560.

2. I have been informed and understand that the last Office Action issued in this application was dated September 26, 2007 and that the Examiner of this application is of the view and stated in the Office Action that the subject matter claimed in this application is considered unpatentable as obvious over Moss *et al.*, *Current Biology* 12:R138-R140 (2002), in view of Yu *et al.*, *J. of Virology* 73:3638-3648 (1999) and Konings *et al.*, *J. of Virology* 66:632-640 (1992) as well as Grad *et al.*, *Molecular Cell* 11:1253-1263 (2003) and Lagos-Quintana *et al.*, *Science* 294:853-858 (2001) in view of Konings *et al.* I make this declaration to provide facts that I believe are probative of the issues raised by the rejection.

3. The subject matter of this application relates to viral miRNA-related nucleic acids. At the time of invention of this application, miRNAs were known to be processed from hairpin structures. In addition, computational methods such as those described by Moss *et al.* and Grad *et al.* had been used to identify miRNAs by taking into account certain structural features of hairpin precursors. However, these computational methods required sequence conservation to be present with previously known miRNAs. All previously known miRNAs were limited to complex multicellular eukaryote organisms, specifically plants and animals. There are great phylogenetic differences existing between complex multicellular eukaryotes and more primitive organisms, which lead to substantial sequence divergences. Due to the computational methods of Moss *et al.* and Grad *et al.* requiring sequence conservation, I would have been skeptical that such methods would be able to identify miRNAs in more primitive organisms such as viruses.

4. Regardless of the method used to identify miRNAs, and although logically, from a functional point of view, one could have thought that viruses can benefit from miRNA, I was skeptical that miRNAs existed in viruses. At the time, miRNAs were believed to be extremely rare within the very large genomes of complex eukaryotes. At comparable prevalence within the genome or non-coding sequences, miRNAs would not be present in a virus because a viral genome and viral non-coding sequences are on the order of 10^3 to 10^6 times smaller than the complex multicellular eukaryotes that were known to contain miRNAs.

5. Yu *et al.* found a hairpin secondary structure in the Bovine viral diarrhea virus (BVDV) genome. Despite such a secondary structure, I would have been skeptical that viruses contain miRNAs. Many secondary hairpin structures were known to exist in viruses, however, each of these structures act in *cis*-related regulation (e.g., translation, initiation, IRES, and PKR inhibition) rather than *trans*-related regulation, such as a miRNA. For these reasons, I would have been skeptical that viruses contain miRNAs.

6. In summary, miRNAs known prior to the invention of this application were limited to complex multicellular eukaryotes. There had been no indication that miRNAs existed in more primitive organisms, such as yeast, bacteria, archibacteria or viruses. In fact, in an estimation of the number of miRNAs in the human genome by one of the leaders in the miRNA field, Lim *et al.*, *Science* 299:1540 (2003) states the belief that miRNAs do not exist in more simple organisms such as yeast. Thus, at the filing date of this application, it was believed in the field that miRNAs did not exist in viruses.

7. Pfeffer *et al.* *Science* 304:734-736 (2004), which was published well after the invention of this application, reports the first public discovery of viral miRNAs. Pfeffer *et al.* was clearly regarded as a significant advance by the scientific community as shown by being published in *Science* and by also meriting a comment in Editor's Choice of *Science*. The editorial comment in *Science* brings attention to the discovery of miRNAs in the "fourth domain of life," indicating that this was recognized as a ground breaking achievement.

8. In accordance with my experience in this field and my knowledge of the state of the art at the time the invention of this application was made, it is clear that the inventors broke with the established teachings in the field to identify miRNAs in simple organisms using computational approaches not requiring sequence conservation. I regard this as a significant advance in the field.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Dated__02/26/08-- By Prof Alik Honigman

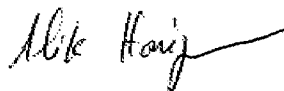


Exhibit A

CV Alik Honigman

CURRICULUM VITAE

Prof. ALIK HONIGMAN

Birth date: 1 January 1942

Marital status: Married, three children

1959-1962: Military service

Academic position: Full Professor

Education

1967, B.Sc., The Hebrew University of Jerusalem, Israel. Faculty of Science. Main Subject: Microbiology and Genetics.

1969, M.Sc., The Hebrew University-Hadassah Medical School, Jerusalem, Israel. Dept. Chemical Microbiology.

Thesis: "Genetic control of the life cycle of Bacteriophage P1"

1970-1975, Ph.D. student, Assistant and Instructor at the, Dept. of Molecular Genetics. The Hebrew University-Hadassah Medical School, Jerusalem, Israel.

Thesis: "Genetics and Biochemical Studies of the early Regulation of Bacteriophage lambda".

1975-1977 McArdle Laboratory for Cancer Research, University Of Wisconsin, Madison, WI - Research Associate in Prof. Szybalski's laboratory.

Positions held

2006 – now Chairman of Planning and Development of the Faculty of medicine of the Hebrew University, Jerusalem

2004- now The Lady Davis Chair in Experimental Medicine and Cancer Research.

- 2003- now Member in the academic council of the David Yelin College
for education in Jerusalem.
- 2000-now Chairman of the Interdepartmental Equipment Unit of the Faculty of
Medicine, the Hebrew University, Jerusalem, Israel.
- 1996- 2000 Dean Assistant for Public Relations, The HU Faculty of Medicine.
- 1966- now Chairman of the scientific advisory board of Promega Biotechnology
Corporation.
- 1995- now Dept. of Virology, The faculty of Medicine, The Hebrew
University, Jerusalem.
- 1994-1995 Promega Corp. and the University of Wisconsin, Visiting Professor of
Molecular Virology
- 1992- 1997 Institute of Microbiology - Head of Curriculum Committee
- 1990-1995 Head of Department of Molecular Genetics, The Hebrew University-
Hadassah Medical School, Jerusalem.
- 1992-1995 Dept. of Molecular Genetics, Hebrew University- Hadassah Medical
School, Associate Professor
- 1983-1992 Dept. of Molecular Genetics, Hebrew University- Hadassah Medical
School, Senior Lecturer
- 1984-1985 NIH, NCI-FCRF, Fredrick, Maryland, Visiting Scientist.
- 1977-1982 Dept. of Molecular Genetics, Hebrew University- Hadassah Medical
School, Lecturer

Books edited

Aids A global Phenomenon (1998) Editors: Morag, A and **Honigman, A**, The Hebrew University of Jerusalem, Akademon, Student Union press.

Publications

1. Olitzki, A., D. Godinger, M. Israeli and **A. Honigman** (1967). Studies on Atypica mycobacteria. Glycols, mono- and polyhydric alcohols as growth Promoting and inhibiting substances. Estratto dal Boll 1st sieroterMilanese 46:5-6
2. Olitzki, A., H. Haas, D. Godinger, M. Israeli and **A. Honigman** (1967). Studies on atypical Mycobacteria in Israel. Path. Microbiol. 30:433-488.
 3. Olitzki, A., D. Godinger, M. Israeli and A. Honigman (1967). In vitro Effects of some chemotherapeutic agents on mycobacteria. Applied Microbiology 15:994-1001.
4. Echols, H., L. Green, A.B. Oppenheim and **A. Honigman** (1973). Role of The cro gene in bacteriophage lambda development. J. Mol. Biol. 80:203-216.
5. Oppenheim, A., **A. Honigman** and A.B. Oppenheim (1974). Interference with phage lambda cro gene function by a colicin-tolerant E. coli mutant. Virology 61:1-10.
6. Oppenheim, A.B., **A. Honigman**, A. Oppenheim and W. Stevens (1975). Interaction between bacteriophage lambda and its bacterial host: regulation Of developmental pathways, in: Dynamic Aspects of Host Parasite Relationships, A. Zuckerman, Editor. A. Halsted Press: New York, Toronto, Israel Universities Press, Jerusalem, pp. 40-55.
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8. **Honigman, A.**, S.L. Hu, R. Chase, and W. Szybalski (1976). 4S oop RNA is a leader sequence for the immunity-establishment transcription in coliphage lambda. Nature 262:112-116.
9. Rosenvold, E. and **A. Honigman** (1977). Mapping of Ava 1 and Xma 1 cleavage sites in bacteriophage lambda DNA including a new technique of DNA digestion in agarose gels. Gene. 2:273-288.
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11. Szybalski, E., M. Fiandt, **A. Honigman**, E. Rosenvold and W. Szybalski (1977). A deletion of the p-Q (nin) region of phage lambda b2mm21 conferring partial N21 independence. Gene. 2:294-296.
12. Fuchs, C., E. Rosenvold, **A. Honigman** and W. Szybalski (1979). A simple method for identifying the palidromic sequences recognized by restriction endonucleases: the nucleotide sequence of the Ava 11 site. Gene. 4:1-23.
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14. Enquist, L., **A. Honigman**, S.L. Hu and W. Szybalski (1979). Expression of int gene function in ColE1 hybrid plasmids carrying the C fragment of bacteriophage lambda. *Virology* 92:557-560.
15. Fuchs, C., E. Rosenvold, **A. Honigman** and W. Szybalski (1980). Identification of palindromic sequences recognized by restrictases, as based on the tabularized sequencing data for seven viral and plasmid DNAs. *Gene*. 10:357-370.
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